IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

KATHERINE CROCKETT, **Plaintiff,** **v.** **LUITPOLD PHARMACEUTICALS, INC.; AMERICAN REGENT, INC.; DAIICHI SANKYO, INC.; DAIICHI SANKYO US HOLDINGS, INC.; and VIFOR (INTERNATIONAL) AG,** **Defendants.**	**CIVIL ACTION** **NO. 19-276**

MEMORANDUM OPINION

This drug product liability case arises out of the alleged injuries Plaintiff Katherine Crockett sustained after being administered Injectafer, an iron-replacement medication used to treat iron deficiency anemia. Plaintiff attributes her injuries to hypophosphatemia ("HPP"), a condition marked by low blood phosphorus levels. In light of the parties' familiarity with the case, further factual background is omitted here.

Pursuant to *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), Defendants seek to exclude certain opinions of nephrologist Dr. Myles Wolf, specifically those regarding:

- "Injectafer's FDA-approved Prescribing Information," *i.e.* labeling;
- "Alleged Systematic Underreporting of Cases of Symptomatic HPP";
- "Clinical Consequences from Injectafer-Induced HPP Remain[ing] Latent for More than One to Two Months";
- "'Persistent' HPP from Injectafer . . . allegedly increase[ing] the risk for clinical complications"; and
- "The alleged 'significant' effects that a single course of Injectafer can have on bone."

For the reasons below, Defendants' motion will be denied.

I. LEGAL STANDARDS

Daubert established a "gatekeeping role" for trial courts in admitting expert testimony. *Oddi v. Ford Motor Co.*, 234 F.3d 136, 144 (3d Cir. 2000) (quoting *Daubert*, 509 U.S. at 597). The *Daubert* standard is codified in Federal Rule of Evidence 702, which provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702; *see Durando v. Trustees of Univ. of Pennsylvania*, 2022 WL 2467080, at *1 (E.D. Pa. July 6, 2022). The rule "embodies a trilogy of restrictions on expert testimony: qualification, reliability, and fit." *Durando*, 2022 WL 2467080, at *1 (quoting *Schneider ex rel. Est. of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003)). The proponent of expert testimony has the burden of establishing its admissibility by a preponderance of evidence. *Oddi*, 234 F.3d at 144 (citing *Daubert*, 509 U.S. at 593 n.10).

A. Qualifications

To satisfy *Daubert*'s qualification requirement, an expert must possess "specialized knowledge regarding the area of testimony." *Betterbox Comm'ns Ltd. v. BB Techs., Inc.*, 300 F.3d 325, 327 (3d Cir. 2002) (internal quotation omitted). "The basis of this specialized knowledge 'can be practical experience as well as academic training and credentials.'" *Waldorf v. Shuta*, 142 F.3d 601, 625 (3d Cir. 1998) (citing *American Tech. Resources v. United States*, 893 F.2d 651, 656 (3d Cir. 1990); and *Hammond v. International Harvester Co.*, 691 F.2d 646, 653 (3d Cir. 1982)). The qualification requirement is generally interpreted "liberally," *Pineda v.*

Ford Motor Co., 520 F.3d 237, 244 (3d Cir. 2008), and "a broad range of knowledge, skills, and training qualify an expert as such." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 741 (3d Cir. 1994) (citation omitted).

B. Reliability

An expert's conclusions must "reliably flow from the facts known to the expert and the methodology used." *Oddi*, 234 F.3d at 146 (citation omitted). "To satisfy the reliability requirement, 'the expert must have good grounds for his or her belief,' not 'subjective belief or unsupported speculation.'" *T.N. Incorporation, Ltd. v. Fid. Nat'l Info. Servs., Inc.*, 2021 WL 5980048, at *2 (E.D. Pa. Dec. 17, 2021) (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d at 742). Beyond the traditional *Daubert* reliability factors, which focus on assessing scientific methods, *see In re Suboxone (Buprenorphine Hydrochloride & Naloxone) Antitrust Litig.*, 2020 WL 6887885, at *3 (E.D. Pa. Nov. 24, 2020), the reliability inquiry may also focus upon an expert's "personal knowledge or experience." *Id.* at *26 (quoting *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 150 (1999)). "The reliability test is flexible and a district court enjoys 'broad latitude when it decides how to determine reliability.'" *Durando*, 2022 WL 2467080, at *2 (quoting *Kumho Tire*, 526 U.S. at 142). When reliability questions go to the weight of an expert's proposed testimony rather than its admissibility, they become an issue suitable for the jury. *See id.* at *4.

C. Fit

"In assessing whether an expert's proposed testimony fits, [the question is] whether the expert testimony proffered is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute." *United States v. Schiff*, 602 F.3d 152, 173 (3d Cir. 2010) (internal quotation, ellipses, and citation omitted). The fit of testimony goes "primarily to relevance."

Daubert, 509 U.S. at 591. Relevancy presents a "relatively low obstacle to clear." *Hausknecht v. John Hancock Life Ins. Co. of New York*, 2022 WL 1664362, at *8 (E.D. Pa. May 25, 2022) (citing *United States v. Ford*, 481 F.3d 215, 219-20 (3d Cir. 2007)). "The Rules of Evidence embody a strong preference for admitting any evidence that may assist the trier of fact." *Pineda*, 520 F.3d at 243 (citation omitted).

II. DISCUSSION

A. Opinions re: Injectafer's Prescribing Information

Defendants contend that Wolf's testimony regarding the adequacy of the content of Injectafer's labeling, specifically the prescribing information, fails to meet any of the three requirements for admissibility.

i. Qualifications

Defendants' objections based on Wolf's lack of experience or expertise (*i.e.*, qualifications) regarding the federal regulations surrounding drug labeling are misplaced: Wolf does not opine on the Injectafter labeling from a regulatory perspective (*e.g.*, whether certain regulations were or were not complied with). Instead, his report draws conclusions about the purported inadequacy of the product labeling from his analysis of medical data and clinical trials (*e.g.*, "There are major flaws in the design, reporting, and interpretation of these pivotal phase III trials that ultimately are reflected in the product labeling[.]"; "[B]y conflating a majority of patients with chronic kidney disease with a minority who had all other causes of iron deficiency anemia, the true risk of hypophosphatemia among different subgroups of patients could not have been accurately ascertained by reviewing the label."). Defendants' objections based on Wolf's lack of regulatory experience do not match the opinions he offers. Otherwise, Defendants expressly "do not challenge Dr. Wolf's qualifications as a nephrologist."

In any case, Wolf is qualified to opine on purported inadequacies in the Injectafer labeling from a physician's perspective in light of his medical expertise, his relevant clinical trial research, and his review of the relevant medical literature. He is a distinguished professor of medicine and chief of the Division of Nephrology in the Department of Medicine at Duke University School of Medicine. He has clinical and research expertise in nephrology and intravenous iron and led clinical trials specifically related to ferric carboxymaltose ("FCM") (the chemical compound in Injectafer) and HPP. And he also manages "patients with iron deficiency anemia and frequently prescribes intravenous iron[.]" While he appears not to prescribe Injectafer specifically, his experience prescribing similar drug treatments, in addition to his expertise and knowledge on iron deficiency and related treatments, is sufficient to qualify him in this regard.

ii. Reliability

Defendants maintain that Wolf cannot reliably opine as to "what all prescribing physicians" know about HPP-related risks or how they would interpret prescribing information in Injectafer's labeling. While doctors generally may not "opine as experts about what all doctors generally consider in making prescription decisions," they may nonetheless "opine on the medical facts and science regarding the risks and benefits of the [] drugs in question and to compare that knowledge with what was provided in the text of labeling and warnings on the [] drugs in question." *In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prod. Liab. Litig.*, 2000 WL 876900, at *11 (E.D. Pa. June 20, 2000). Wolf's proffered testimony fits within this permissible scope.

Defendants also contend that Wolf's opinions about how other physicians would interpret the Injectafer prescribing information (*i.e.*, the purported inadequacy of the labeling information)

is "based on his personal beliefs and unfounded assumptions." This is not the case. Wolf expressly relied on his "clinical and research expertise in the areas of internal medicine, nephrology, phosphorus metabolism, intravenous iron, and their interconnections," as well as his direct experience with clinical trials related to HPP. Not only that, he conducted a "detailed review of the literature" to support the opinions in his report.

iii. Fit

Wolf's labeling opinions have a clear connection with the "particular disputed factual issues in the case." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d at 743 (quoting *United States v. Downing*, 753 F.2d 1224, 1237 (3d Cir. 1985)). Plaintiff brings negligence claims predicated on Defendants' purported failure to adequately warn of Injectafer's risks of HPP in the drug's labeling and to perform adequate testing of the drug product.

Defendants' objections to the fit of Wolf's testimony based on the learned intermediary doctrine, Plaintiff's prescribing physician's testimony, and FDA regulatory requirements for label changes do not negate the relevance of his testimony; instead, such arguments are better suited for the adversarial process, such as for use during cross-examination. *See, e.g.*, *King Drug Co. of Florence, Inc. v. Cephalon, Inc.*, 2015 WL 5783603, at *9 (E.D. Pa. Oct. 5, 2015) (concluding that challenges to the fit of expert opinions did not warrant exclusion and were "more appropriately addressed through cross-examination or competing expert testimony").

B. Opinions re: Alleged Systematic Underreporting of Symptomatic HPP

Defendants contend that there "is no reliable methodology or data supporting Dr. Wolf's underreporting theory," objecting to his conclusion that symptomatic hypophosphatemia may have been underreported in two of Defendants' clinical trials conducted prior to FDA approval of Injectafer as well as in the broader literature. Defendants focus on Wolf's language in his report

referring to this theory as a "hypothesis" and his statement that a lack of information about hypophosphatemia provided to the "site investigators" undertaking those clinical trials "*may have* led [them] . . . to systematically underreport hypophosphatemia as an adverse event and adverse drug reaction caused by FCM" (emphasis added)—contending that such "equivocation" is impermissible in expert opinions.

Wolf reliably bases his underreporting theories on his review of the medical literature, the protocols governing the clinical tests of Injectafer, and his own experience as a clinical researcher. Moreover, while Wolf refers in his deposition testimony to his theory of underreporting as a "hypothesis" and in his report as something that "may have" occurred with respect to the clinical trials for Injectafer, he elsewhere describes the particular "[c]hallenges to making the diagnosis of hypophosphatemia" based on his experience and research that would contribute to such underreporting, including the need to order specific tests, misattribution of non-specific symptoms of HPP, and lack of experience regarding HPP among clinicians who administer intravenous iron. Additionally, Wolf observes in respect to underreporting that while "it's very hard to generate evidence of something that doesn't happen," as compared to reported rates "there's way more hypophosphatemia that occurs in response to being administered this drug. And there are many, many case reports of severe complications as a result of that." By this, Wolf appears to be referring to his report's conclusion that "[a]mong patients with normal kidney function, FCM causes hypophosphatemia in at least 50% and as many as 75% of patients who receive the drug." In this light, Wolf's testimony is not mere conjecture but an assessment of the likelihood of underreporting. As he states elsewhere in the report, "[t]here is a lack of knowledge about hypophosphatemia in the medical community and specifically among the specialties that most commonly administer FCM. As a result, cases of hypophosphatemia are

likely underreported and may go undiagnosed even in the presence of the clinical consequences described [elsewhere in the report]." This conclusion, while it does not assign a particular rate to the underreporting Wolf hypothesizes occurs (if assigning a particular rate to underreporting would be possible), is nonetheless based on good grounds—namely Wolf's extensive research and experience.

Overall, Defendants' objections go to the weight of Wolf's testimony on underreporting, making them better suited for cross-examination. *See Durando*, 2022 WL 2467080, at *4 (stating that arguments about reliability that go to the weight of proposed testimony are generally a matter for the jury).

C. Opinions re: Latent Clinical Consequences from Injectafer-Induced HPP and "Persistent" HPP Increasing the Risk of Clinical Complications

Defendants next object to Wolf's opinions that past clinical trials have not "studied the clinical consequences of FCM-induced hypophosphatemia," in part due to the "latency period between treatment with FCM and potential clinical consequences of it." Specifically, Wolf states in his report that the latency period is "longer than the duration of the follow-up period of trials in the area, which typically were limited to 1-2 months" and, as a result, patients in trials cannot accumulate enough time to develop the adverse effects that occur in real world practice[.]" Defendants focus on Wolf's methodology and maintain that Wolf offers "no data to support his opinion," pointing specifically to the relevant section of Wolf's report and the absence of any citation therein. Defendants also disagree with the substance of Wolf's opinion by citing to other studies, disputing the length of certain Injectafer clinical trials, and arguing that Wolf's opinion in this regard is inconsistent with other aspects of his report, specifically his opinions on specific causation.

Wolf's methodology underlying this opinion, as with those above, is sufficient: as with

others in the report, the opinion on latent consequences of HPP resulting from Injectafer is based on Wolf's extensive clinical research experience and his review of the relevant medical literature, including the numerous articles listed as references for his report's opinions. To the extent Defendants dispute the substance of Wolf's report, that is a matter for questioning at trial. *See, e.g.*, *Durando*, 2022 WL 2467080, at *4.[1]

While Defendants maintain further that Wolf's opinions regarding the latent consequences from HPP associated with Injectafer use also do not "fit" the case inasmuch as they purportedly conflict with his specific causation opinions, they are nonetheless relevant to the case, and Defendants can point to any purported inconsistency during cross-examination.[2]

D. Opinions re: Significant Injectafer Effects on Bone

Finally, Defendants object to Wolf's opinion "that a single course of Injectafer 'can have significant effects on bone.'" Specifically, Wolf states, within his discussion of a "pair of identically designed randomized clinical trials" he led, that "[i]n the aggregate, these bone data suggest that even a single course of FCM can have significant effects on bone, which helps explain why repeated dosing of FCM has been associated with osteomalacia and fractures."

Defendants contend that Wolf does not have any supporting data for this opinion. But the report that Defendants find fault with states expressly:

[1] The same conclusion applies to Wolf's opinions regarding persistent HPP and its increased risk for clinical complications, which Defendants similarly object to on the basis of methodology.

[2] Additionally, the Court will not consider Defendants' argument that Wolf's latency opinions are irrelevant on the basis Plaintiff did not suffer such latent consequences because it was only raised in their reply brief. *See, e.g.*, *Laborers' Int'l Union of N. Am., AFL-CIO v. Foster Wheeler Energy Corp.*, 26 F.3d 375, 398 (3d Cir. 1994) ("An issue is waived unless a party raises it in its opening brief, and for those purposes a passing reference to an issue . . . will not suffice to bring that issue before this court." (internal quotation and citation omitted)).

> Thus, an important finding of these trials is that ferric carboxymaltose induced increases in intact fibroblast growth factor 23 and its downstream metabolic consequences may have significant effects on bone, as evidenced by increased total and bone-specific alkaline phosphatase and decreases in N-terminal propeptide of type 1 collagen, and carboxyterminal collagen crosslinks. The change in alkaline phosphatase, which is consistent with the pattern observed in patients with osteomalacia,33,34 provides new evidence that even a single course of ferric carboxymaltose may adversely affect the skeleton and may help explain why repeated dosing of ferric carboxymaltose has been associated with osteomalacia and fractures.

Moreover, Defendants do not address the other medical literature cited in the relevant portion of Wolf's report as sources of support for his conclusion.

To the extent Defendants have disputes concerning the data underlying the report they find fault with, such concerns are better suited for cross-examination. For instance, while Defendants contend that Wolf suggests that the clinical significance of the underlying data supporting this conclusion may be limited by pointing to scattered portions of his testimony regarding related "bone biomarker" data, their argument does not demonstrate that Wolf lacks good grounds for his opinion. Moreover, it is important to emphasize that Wolf does not appear to opine that a single course of Injectafer could cause "osteomalacia" or "fractures"; his report expressly states that only "repeated dosing of FCM" has been "associated" with such consequences. So to the extent Defendants object to his conclusions on that basis, their concern is misplaced.

Finally, while Defendants argue that Wolf's opinions on Injectafer's effects on bone are irrelevant on the basis Plaintiff states in her own *Daubert* motion (ECF No. 301) that "Plaintiff has not alleged any long-term bone injury secondary to her use of FCM" and "Plaintiff is not alleging a bone injury," Defendants raise this argument only in their reply brief—for which reason it will not be considered for purpose of disposing of the instant motion. *See Laborers' Int'l Union of N. Am.*, 26 F.3d at 398. Moreover, it is unclear the extent to which Plaintiff,

through such statements, concedes that bone-related effects of Injectafer are irrelevant to her claims, so the Court is not prepared to preclude Wolf's opinions on the drug's effects on bone on that account alone.

Accordingly, Defendants' motion shall be denied. An appropriate order follows.

BY THE COURT:

/s/Wendy Beetlestone, J.

WENDY BEETLESTONE, J.